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Lead Optimization Studies on Novel Quinolones Derivatives as CYP-450 Inhibitor by using *In-Silico* Modulation

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ABSTRACT

The *In-silico* studies considered as complementary to in vivo and in vitro biological studies are performed by using a computer and are playing increase larger and more important role in drug discovery and development. We describe here in *In-silico* study of various hypothetical Quinolines and their interactions with CYP450 enzymes by computational methods including chem draw ultra, Avogadro and ochem database software methods. We worked on a chemical reaction scheme of Quinolines and we prepared different 20 Quinolines derivatives. The CYP450 super family of heme enzymes plays an important role in the metabolism of a large number of endogenous and exogenous compounds including most of the drugs currently on the market. Comprehensive studies of the quantum approaches on the quinolines derivatives like QD1, QD8 and QD13 was found to be CYP450 enzymes inhibitors interactions. The quantum approaches by lead optimization will require further studies; the data reported in this work may be helpful guide for medicinal chemist who is working in this area.

Keywords: In-silico, Quinolone, CYP450 inhibitor

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INTRODUCTION

Quinolines agents exhibit a bicyclic aromatic core, containing a carbon at the 8th position, yielding a true quinolones, or nitrogen, and provide a ring system technically termed as naphthyridone. In common usage, both quinoline and naphthyridone structures are encompassed in the class descriptor quinolones antibacterial agents ^[1].

The first generation quinolones compounds generally displayed increased Gram-negative activity over nalidixic acid, but lacked useful activity against Gram-positive cocci, pseudomonas aeruginosa, and anaerobes. They were, however, generally well absorbed after oral administration and attained high concentrations in the urinary tract, making them useful therapeutically for treatment of urinary tract infections. In the secondgeneration quinolones, the piperazine ring remains relatively undisturbed, except for alkylation on the distal nitrogen or, less frequently, on the ring carbons.

The second-generation compounds are characterized by good to excellent Gram-negative activity, with ciprofloxacin exhibiting the strongest Gram-negative spectrum. The third- and fourth-generation quinolones are characterized by increased structural novelty and complexity, which has resulted in new and useful characteristics ^[2, 3]. *In-silico* literally Latin for "in silicon", alluding to the mass use of silicon for semiconductor computer chips is an expression used to mean performed on computer or via computer simulation. The phrase was coined in 1989 as an allusion to

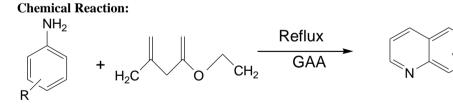
the Latin phrases in vivo, in vitro, and in situ, which are commonly used in biology and refer to experiments done in living organisms, outside of living organisms, and where they are found in nature, respectively ^[4]. Computer-aided drug design is the use of computer systems to aid in the creation, modification, analysis, or optimization of a design. CADD software is used to increase the productivity of the designer, improve the quality of design, improve communications through documentation, and to create a database for manufacturing ^[5].

CADD output is often in the form of electronic files for print, machining, or other manufacturing operations. The term CADD is also used. Its use in designing electronic systems is known as electronic design automation. In mechanical design it is known as mechanical design drafting, automation or computer-aided which includes the process of creating a technical drawing with the use of computer software ^[6]. Inhibitors of the CYP450 enzymes have more important role in the treatment of several disease conditions such as numerous cancers and anti fungal interactions in addition to their critical role in drug-drug interaction. Understanding the key structure features of inhibitors responsible for their inhibition potency has been essential for CYP450 inhibitors design and development [7].

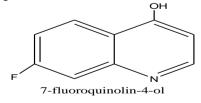
MATERIAL AND METHODS

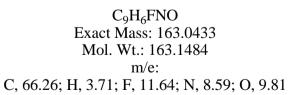
Software used for lead optimization: Chem Draw Ultra8.0, Avogadro, OCHEM database.

[8]

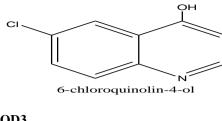


20 novel quinolones derivatives with elemental analysis: QD1.

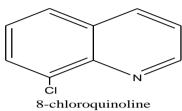




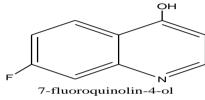
QD2.





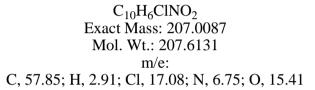


QD4.



C₉H₆ClNO Exact Mass: 179.01379 Mol. Wt.: 179.60304 m/e: C, 60.19; H, 3.37; Cl, 19.74; N, 7.80; O, 8.91

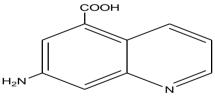
C₉H₆ClN Exact Mass: 163.01888 Mol. Wt.: 163.60364 m/e: C, 66.07; H, 3.70; Cl, 21.67; N, 8.56



OD5.

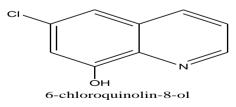


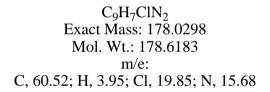




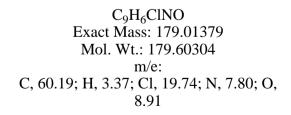
7-aminoquinoline-5-carboxylic acid

QD7.





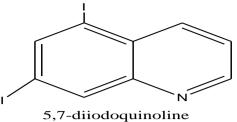
 $C_{10}H_8N_2O_2$ Exact Mass: 188.05858 Mol. Wt.: 188.18272 m/e: C, 63.82; H, 4.28; N, 14.89; O, 17.00

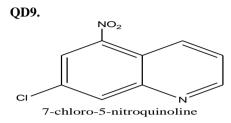


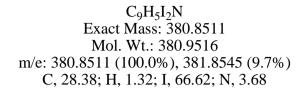
QD8.

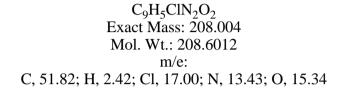
QD10.

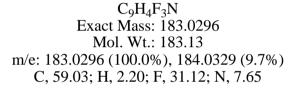
OD11.

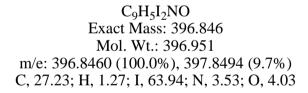




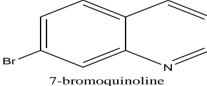








QD12.

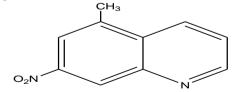


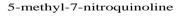
5,7-diiodoquinolin-8-ol

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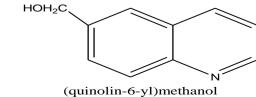
5,7,8-trifluoroquinoline

QD13.





QD14.



m/e: C, 51.96; H, 2.91; Br, 38.41; N, 6.73

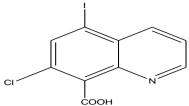
C₉H₆BrN Exact Mass: 206.9684 Mol. Wt.: 208.0546

C₁₀H₈N₂O₂ Exact Mass: 188.0586 Mol. Wt.: 188.1827 m/e: C, 63.82; H, 4.28; N, 14.89; O, 17.00

C₁₀H₉NO Exact Mass: 159.0684 Mol. Wt.: 159.1846 m/e: 159.0684 (100.0%), 160.0718 (10.8%) C, 75.45; H, 5.70; N, 8.80; O, 10.05

180

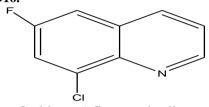
QD15.



C₁₀H₅ClINO₂ Exact Mass: 332.9053 Mol. Wt.: 333.5097 m/e: C, 36.01; H, 1.51; Cl, 10.63; I, 38.05; N, 4.20; O, 9.59

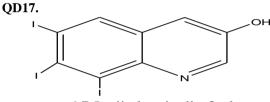
7-chloro-5-iodoquinoline-8-carboxylic acid

QD16.



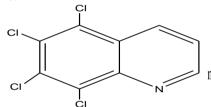
8-chloro-6-fluoroquinoline

C₉H₅ClFN Exact Mass: 181.0095 Mol. Wt.: 181.5941 m/e: C, 59.53; H, 2.78; Cl, 19.52; F, 10.46; N, 7.71

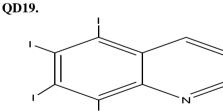


6,7,8-triiodoquinolin-3-ol

QD18.

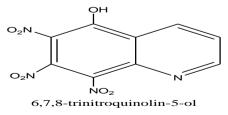


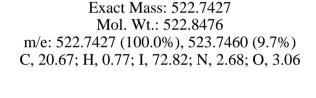




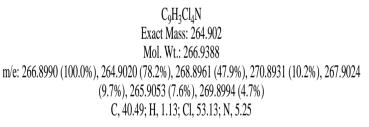
5,6,7,8-tetraiodoquinoline

QD20.





C₉H₄I₃NO

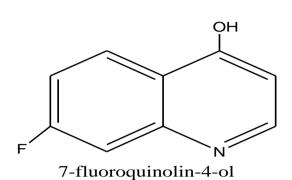


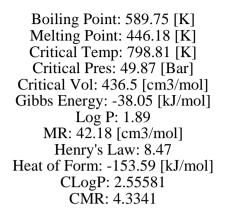
C₉H₃I₄N Exact Mass: 632.6444 Mol. Wt.: 632.7447 m/e: 632.6444 (100.0%), 633.6478 (9.7%) C, 17.08; H, 0.48; I, 80.22; N, 2.21

C₉H₄N₄O₇ Exact Mass: 280.008 Mol. Wt.: 280.1507 m/e: 280.0080 (100.0%), 281.0114 (9.7%), 281.0050 (1.5%), 282.0122 (1.4%) C, 38.59; H, 1.44; N, 20.00; O, 39.98

RESULT AND DISCUSSION

QD1.





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	Properties							? >	
	Element	Туре	Valence	Formal Charge	Partial Charge	X (Å)	Y (Å)	Z (Å)	
Atom 1	С	Car	3	0	0.077	0.04582	-0.66861	0.00677	
Atom 2	с	Car	3	0	0.042	-0.01977	0.74195	0.00009	
Atom 3	с	Car	3	0	-0.046	-1.27667	1.38618	-0.01943	
Atom 4	с	Car	3	0	-0.026	-2.45177	0.64083	-0.03188	
Atom 5	с	Car	3	0	0.125	-2.36891	-0.74233	-0.02350	
Atom 6	с	Car	3	0	-0.000	-1.13804	-1.38900	-0.00413	
Atom 7	N	Nar	2	0	-0.255	1.21264	-1.33693	0.02312	
Atom 8	с	Car	3	0	0.032	2.35880	-0.62248	0.03270	
Atom 9	с	Car	3	0	-0.001	2.40928	0.75695	0.02883	
Atom 10	С	Car	3	0	0.127	1.20106	1.43784	0.01315	
Atom 11	F	F	1	0	-0.205	-3.49451	-1.46867	-0.03473	
Atom 12	0	03	2	0	-0.506	1.19048	2.80848	0.01046	
Atom 13	н	н	1	0	0.063	-1.33270	2.47287	-0.02561	

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	Bond 3	C-C	C3	C4	1	No	1.39161				
	Bond 4	C-C	C4	C5	2	No	1.38566		4		
	Bond 5	C-C	C5	C6	1	No	1.39054	7.0)	
	Bond 6	C-C	C1	C6	2	No	1.38585				
	Bond 7	C-N	C1	N	1	No	1.34476				
	Bond 8	N-C	N	C7	2	No	1.35063				
	Bond 9	C-C	C7	C8	1	No	1.38036				
	Bond 10	C-C	C8	C9	2	No	1.38695				
	Bond 11	C-C	C2	C9	1	No	1.4053				
	Bond 12	C-F	C5	F	1	No	1 33966				
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Bond Properties with 3D View

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	Angle 1	ccc	C2	C1	C6	118.6545				
	Angle 2	CCN	C2	C1	N	122.4659				
	Angle 3	CCN	C6	C1	N	118.8796				
	Angle 4	ccc	C1	C2	C3	119.8009				
	Angle 5	CCC	C1	C2	C9	117.0168				
	Angle 6	ccc	C3	C2	C9	123.1822				
	Angle 7	ccc	C2	C3	C4	120.4795				
	Angle 8	ссн	C2	C3	H1	120.0904				
	Angle 9	ссн	C4	C3	H1	119.4301				
	Angle y	ССН	C4	G	HI	119,4301				

Angle Properties with 3D View

Ochem database prediction results as CYP450 inhibitor:

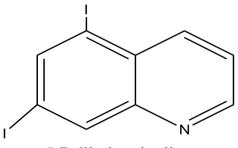
LogPow (ALogPS 3.0) = $1.9 \text{ Log unit } \pm 0.77 \text{ (ASNN-STDEV} = 0.14, estimated RMSE = 0.39)$

Aqueous Solubility (ALogPS 3.0) = $2.1 -\log (mol/L) \pm 1.41$ (ASNN-STDEV = 0.30, estimated RMSE = 0.72) Log (IGC50-1) (Toxicity against T. Pyriformis) = $0.48 -\log (mmol/L) \pm 1.07$ (ASNN-STDEV = 0.57, estimated RMSE = 0.55)

CYP450 modulation= inhibitor (94.0% accuracy)

Melting Point (Melting Point prediction (best Estate)) = $170 \degree C$ Aqueous Solubility (ALOGPS 2.1 logS) = $-1.7 \log (mol/L)$ LogPow (ALOGPS 2.1 logP) = 2.2 Log unit

QD8.



5,7-diiodoquinoline

Boiling Point: 701.12 [K] Melting Point: 462.51 [K] Critical Temp: 924.56 [K] Critical Pres: 40.11 [Bar] Critical Vol: 578.5 [cm3/mol] Gibbs Energy: 417.99 [kJ/mol] Log P: 4.83 MR: 64.95 [cm3/mol] Henry's Law: 5.82 Heat of Form: 362.1 [kJ/mol] CLogP: 4.36005 CMR: 6.7783

Atom 12 I I 1 0 -0.043 1.40309 3.53723 0.10009	isplay Type	9		l∄ × Vie	ew 1				
Element Type Valence Formal Charge X(A) V(A) Z(A) A Atom 1 C Car 3 0 0.073 -0.0507 -0.05171 -0.05176 Atom 2 C Car 3 0 0.073 -0.0507 -0.05171 -0.05176 Atom 2 C Car 3 0 0.014 -0.0055 0.7592 -0.0584 Atom 3 C Car 3 0 0.024 1.23943 1.43548 0.02028 Atom 5 C Car 3 0 0.016 2.44066 0.02372 -0.02372 Atom 6 C Car 3 0 -0.023 1.23937 -1.34047 -0.05792 Atom 7 N Nar 2 0 -0.255 -1.12746 -0.05872 Atom 7 N Nar 2 0 0.028 -2.31662 -0.61799 -0.08792 Atom 10 C Car 3				1 ⁵⁰ ~					
Lemment Type Type <thtype< th=""> Type Type <</thtype<>	🛎 Atom	Properties							?
C Car 3 C Data Data <thdata< th=""> <thdata< th=""> <thdata< th=""></thdata<></thdata<></thdata<>		Element	Туре	Valence	Formal Charge	Partial Charge	× (Å)	Y (Å)	Z (Å)
Atom 3 C Car 3 C 0.024 1.23943 1.4348 0.02254 Atom 4 C Car 3 0 0.024 1.23943 1.4348 0.02254 Atom 4 C Car 3 0 0.024 1.23943 1.4348 0.02254 Atom 5 C Car 3 0 0.016 2.41908 0.02572 0.02372 Atom 6 C Car 3 0 -0.0255 -1.1246 -1.9477 0.09324 Atom 7 N Nar 2 0.024 -0.255 -1.1246 -1.9477 -0.09324 Atom 6 C Car 3 0 0.0248 -2.31622 -0.7579 -0.08792 Atom 10 C Car 3 0 -0.0255 -1.1246 -0.0493 Atom 10 C Car 3 0 -0.0434 -2.4402 0.0419 -0.0494 Atom 10 C Car 3 0 -0.0444 4.20126 -1.72674 -0.0419 Atom 11 <td>Atom 1</td> <td>С</td> <td>Car</td> <td>3</td> <td></td> <td>0.073</td> <td>-0.00507</td> <td>-0.65711</td> <td>-0.05176</td>	Atom 1	С	Car	3		0.073	-0.00507	-0.65711	-0.05176
Atom C Car 3 C 0.003 7.12948 0.0026 Atom C Car 3 0 0.003 2.44666 0.02948 0.00237 Atom C Car 3 0 0.016 2.44666 0.02372 -0.02372 Atom C Car 3 0 -0.023 1.13947 -0.03572 Atom N Na 2 0 -0.2372 -1.13246 -0.05792 Atom C Car 3 0 0.026 -1.12246 -1.03947 -0.05792 Atom C Car 3 0 0.028 -2.31622 -0.05799 -0.08796 Atom C Car 3 0 0.028 -2.31622 -0.05792 -0.08796 Atom C Car 3 0 -0.043 1.2409 1.37387 -0.0849 Atom I I 0 -0.044 1.2429 0.40	Atom 2	с	Car	3		0.014	-0.00955	0.75692	-0.00854
Atoms C Car 3 0 0.016 2.41908 -0.65727 -0.02572 Atoms C Car 3 0 0.0161 2.41908 -0.65727 -0.02572 Atoms C Car 3 0 -0.023 1.2357 -1.33607 -0.0592 Atoms C Car 3 0 -0.025 -1.12740 -1.39477 -0.09932 Atoms C Car 3 0 -0.025 -1.12740 -0.09932 Atoms C Car 3 0 -0.0250 -1.12740 -0.09932 Atoms C Car 3 0 -0.0250 -1.23607 -0.08932 Atom C Car 3 0 -0.0500 -1.28905 1.37877 -0.08932 Atom I I 1 0 0.0493 1.37937 -0.0491 Atom H I I 0.0491 3.53723 0.10099 <td>Atom 3</td> <td>с</td> <td>Car</td> <td>3</td> <td></td> <td>0.024</td> <td>1.23943</td> <td>1.43548</td> <td>0.02928</td>	Atom 3	с	Car	3		0.024	1.23943	1.43548	0.02928
Atom 6 C Car 3 0 0.002 1.20307 0.0372 Atom 7 N Nar 2 0 0.0223 1.20307 0.0372 Atom 7 N Nar 2 0 0.0223 1.123607 0.09932 Atom 8 C Car 3 0 0.0224 2.3162 0.0759 0.0876 Atom 9 C Car 3 0 0.0214 2.3172 0.0876 Atom 10 C Car 3 0 0.0214 1.2387 -0.0830 Atom 11 I I 1 0 0.0504 1.2387 -0.04830 Atom 12 I I 1 0 0.0644 4.20126 -1.72674 -0.04191 Atom 12 I H H 0.064 3.33667 1.23642 0.04807	Atom 4	с	Car	3		-0.035	2.44606	0.72948	0.02085
Atom 7 N Nar 2 0 -0.255 -1.1274 -1.39471 -0.0825 Atom 8 C Car 3 0 0.025 -1.1274 -0.0876 Atom 9 C Car 3 0 0.028 -2.3162 -0.0759 -0.0876 Atom 9 C Car 3 0 -0.0493 -2.4402 0.61249 -0.0489 Atom 10 C Car 3 0 -0.0493 1.2346 -0.0493 -0.0494 Atom 11 I 1 0 -0.0444 4.20126 -1.72674 -0.0493 Atom 12 I I 1 0 -0.0444 3.53723 0.10099 Atom 12 H H 0.0644 3.39667 1.2542 0.04807	Atom 5	с	Car	3		0.016	2.41908	-0.65727	-0.02372
Atom 8 C Car 3 0 0.028 7.03739 0.00573 Atom 8 C Car 3 0 0.024 -2.31622 -0.07579 -0.04763 Atom 10 C Car 3 0 -0.043 -2.4862 0.8124 -0.04893 Atom 11 I 1 0 -0.044 4.20126 -1.712674 -0.04191 Atom 12 I I 1 0 -0.043 1.40309 3.33723 0.10099 Atom 12 H H H 0.064 3.39667 1.2542 0.04807	Atom 6	с	Car	3		0 -0.023	1.20357	-1.33607	-0.05792
Atom C Car 3 0 0.0043 2.24462 0.61249 -0.00840 Atom C Car 3 0 -0.0043 5.24462 0.61249 -0.00840 Atom C Car 3 0 -0.0043 1.37367 -0.00840 Atom I I 1 0 -0.0443 4.20126 -1.72674 -0.04191 Atom I I 0 0.0643 1.40309 5.53723 0.10009 Atom H H 1 0 0.0643 3.39667 12.5642 0.04007	Atom 7	N	Nar	2		0 -0.255	-1.12746	-1.39477	-0.08932
Atom 10 C Car 3 0 0.005 1.2360 0.0105 0.0000 Atom 11 I I 1 0 -0.050 -1.28305 1.37387 -0.0840 Atom 12 I I 1 0 -0.043 1.40309 3.5372 0.0009 Atom 12 I H H 0 0.0644 3.39667 1.2564 0.04907	Atom 8	с	Car	3		0.028	-2.31622	-0.75799	-0.08776
Atom 11 I </td <td>Atom 9</td> <td>с</td> <td>Car</td> <td>3</td> <td></td> <td>0 -0.043</td> <td>-2.44602</td> <td>0.61249</td> <td>-0.04893</td>	Atom 9	с	Car	3		0 -0.043	-2.44602	0.61249	-0.04893
Atom 12 I I 1 0 -0.043 1.40309 3.33723 0.10009 Atom 13 H H 1 0 0.064 3.39667 1.25642 0.04807	Atom 10	с	Car	3		0 -0.050	-1.28305	1.37387	-0.00840
Atom 13 H H 1 0 0.064 3.39667 1.25642 0.04007	Atom 11	1.00	1	1		0 -0.044	4.20126	-1.72674	-0.04191
	Atom 12	1.00	1.00	1		0 -0.043	1.40309	3.53723	0.10009
↓	Atom 13	н	н	1		0.064	3.39667	1.25642	0.04807
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Bond 4 C-		:4	C5	2	No	1.38773				
Bond 5 C-		5	C6	1	No	1.39263				
Bond 6 C-		-1	C6	2	No	1.3863		1		
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Atom Properties with 3D view

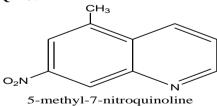
Angle Properties with 3D view

Ochem database prediction results as CYP450 inhibitor:

LogPow (ALogPS 3.0) = 4.6 Log unit \pm 1.50 (ASNN-STDEV = 0.87, estimated RMSE = 0.76) Aqueous Solubility (ALogPS 3.0) = 5 -log (mol/L) \pm 1.41 (ASNN-STDEV = 0.81, estimated RMSE = 0.72) Log (IGC50-1) (Toxicity against T. Pyriformis) = 1.1 -log (mmol/L) \pm 1.07 (ASNN-STDEV = 1.05, estimated RMSE = 0.55) CYP450 modulation = inhibitor (83.0% accuracy)

 $\frac{CYP450 \text{ modulation} = \text{infibitor} (83.0\% \text{ accuracy})}{\text{Melting Point (Melting Point prediction (best Estate))} = 150 \text{ °C}}$ Aqueous Solubility (ALOGPS 2.1 logS) = -4.3 log (mol/L)

QD13.

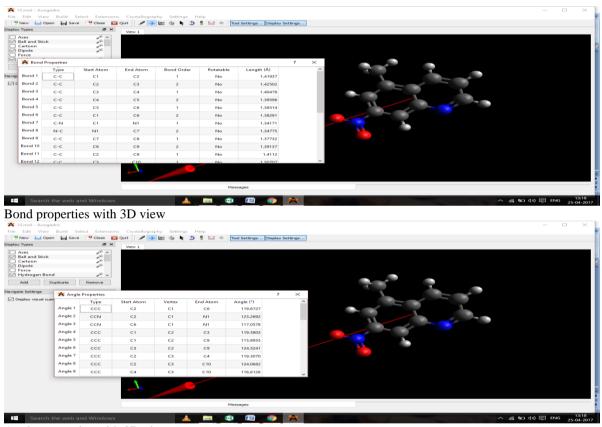


Log P: 2.5 Henry's Law: 3.48 CLogP: 2.406 CMR: 5.2408

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	Element	Туре	Valence	Formal Charge	Partial Charge	× (Å)	Y (Å)	Z (Å)					
Atom 14	0	0-	1	-1	-0.576	4.73123	-0.69915	-0.11017					
Atom 7	N	Nar	2	0	-0.255	-1.11116	-1.42996	-0.08165					
Atom 10	с	Car	3	0	-0.051	-1.30411	1.33834	-0.02148					
Atom 9	с	Car	3	0	-0.043	-2.45601	0.55863	-0.05492					
Atom 11	с	C3	4	0	-0.039	1.29592	2.96915	0.06057					
Atom 3	с	Car	3	0	-0.035	1.20259	1.46546	0.02234					
Atom 2	с	Car	3	0	0.004	-0.02487	0.74254	-0.01564					
Atom 4	с	Car	3	0	0.019	2.41714	0.76003	-0.00292					
Atom 20	н	н	1	0	0.028	0.33896	3.46560	0.22608					
Atom 21	н	н	1	0	0.028	1.70865	3.33814	-0.88420					
Atom 22	н	н	1	0	0.028	1.95444	3.27934	0.87980					
Atom 8	с	Car	3	0	0.028	-2.30809	-0.81045	-0.08225					
Atom 13	0	02	1	0	0.041	3.64372	-2.60340	-0.08788					





Angle properties with 3D view

Ochem database results prediction as CYP450 inhibitor:

LogPow (ALogPS 3.0) = 1.3 Log unit \pm 0.77 (ASNN-STDEV = 0.34, estimated RMSE = 0.39) Aqueous Solubility (ALogPS 3.0) = 2 -log (mol/L) \pm 1.41 (ASNN-STDEV = 0.50, estimated RMSE = 0.72)

Log (IGC50-1) (Toxicity against T. Pyriformis) = - 0.38 -log (mmol/L) \pm 1.07 (ASNN-STDEV = 1.10, estimated RMSE = 0.55)

<u>CYP450 modulation= inhibitor (89.0% accuracy)</u> Melting Point (Melting Point prediction (best Estate)) = $210 \text{ }^{\circ}\text{C}$

Aqueous Solubility (ALOGPS 2.1 logS) = -2.8 log (mol/L)

LogPow (ALOGPS 2.1 logP) = 2.4 Log unit

We describe here in In-silico study of various hypothetical Quinolines and their interactions with CYP450 enzymes by computational methods including CHEM DRAW ULTRA, AVAGARDO, and OCHEM database software methods. We worked on a chemical reaction scheme of Quinolines and I prepared different 20 Quinolines derivatives. A Brief computational study was carried out over 20 designed Quinolines derivatives using various software programmes with the goal of identifying potential and clinically significant CYP450 molecules that are inhibitors. Comprehensive of Quantum studies the

Approaches on the Quinolines derivatives like derivative-1, derivative-8, and derivative-13 were found to be CYP450 enzymes inhibitors interactions. The design and development of potent and selective inhibitors for individual CYP enzymes seems to be an achievable target.

CONCLUSION

The *In-silico* evaluation conforms that the compound had, "Drug like" properties but did not give information of sufficient value to discriminate between compounds. Lead optimization efforts are produced a fully optimized drug candidate ready for pre-clinical development studies. SAR and 3D-QSAR represent important tools in understanding the interaction of inhibitors with the active sites of the CYP enzymes. Two approaches to QSAR

methods used for predicting the metabolism of substrate and inhibitors by CYP have been detailed in this project work. Computational methods including CHEM DRAW ULTRA, for chemical structure drawing, AVAGADRO for molecular editor and visualization tools, and OCHEM DATA BASE for prediction of QSAR based on CYP450 inhibitors studies including other physic-chemical properties of candidate molecules. The recent successes of Quinolines as anti-inflammatory, antimicrobial and anti-cancers have further highlighted the importance of this class in medicinal chemistry. The quantum approaches by lead optimization will require further studies; the data reported in this work may be helpful guide for medicinal chemist who is working in this area.

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